HEALTH EFFECTS OF OZONE EXPOSURE IN ASTHMATICS

A R B CONTRACT NO. 4-191

SEPTEMBER 13, 1974 *through* NOVEMBER 30, 1975

FINAL REPORT

STATE OF CALIFORNIA
AIR RESOURCES BOARD
SACRAMENTO, CALIFORNIA 95814

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ABSTRACT

Health effects of ozone exposure under conditions simulating ambient photochemical pollution episodes have been investigated in volunteer subjects known or suspected to be hyperreactive to inhaled irritant substances. Twenty-five individuals were exposed to approximately 0.2 ppm O_3 and/or approximately 0.4 ppm O_3. Six of these were clinical asthmatics; the others had histories of one or more of the following: rare asthmatic symptoms, upper-respiratory allergy, subjective respiratory sensitivity to photochemical pollution exposure, mild obstructive pulmonary-function abnormality.

The group exposed to 0.4 ppm showed small but significant ($P<.05$) changes in pulmonary function and highly significant ($P<.005$) increases in respiratory symptoms (expressed as a semiquantitative score) and changes in blood biochemical measures. The group exposed to 0.2 ppm showed significant blood biochemical changes ($P<.05$), but no significant changes in symptoms or pulmonary function. Two asthmatic individuals did, however, develop exposure-related symptoms and function changes at 0.2 ppm.

These results suggest that at least some asthmatics are markedly more sensitive to O_3 than normals and may suffer noticeable health effects at concentrations near 0.2 ppm. Most nonasthmatic Los Angeles residents tested tolerate exposure to 0.4 ppm, but some nonresidents react severely to 0.4 ppm, suggesting that adaptation to chronic ambient oxidant exposure develops in relatively healthy Los Angeles residents.

This report was submitted in fulfillment of Contract No. 4-191 by Professional Staff Association of Rancho Los Amigos Hospital, Inc., under sponsorship of the California Air Resources Board. Work was completed 1 December 1975.

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CONCLUSIONS

While the number of subjects studied is too small to allow generalization to larger populations, the results strongly suggest that asthmatics are more reactive to ozone exposure than normal individuals. Most normal Southern California residents appear to tolerate exposure to 0.4 ppm O_3* for two hours with intermittent light exercise without detectable change in pulmonary function and with only mild respiratory symptoms, if any. Asthmatics, however, are likely to experience measurable decrement in function and respiratory symptoms sufficient to restrict normal activity when exposed to 0.4 ppm, and some may be affected at 0.2 ppm. Some individuals in apparently normal health living in areas with little ambient oxidant pollution show more marked response to 0.4 ppm than do normal Southern California residents, suggesting that biological adaptation develops in normal Southern Californians in response to chronic ambient oxidant exposure.

Blood biochemical measures, particularly red cell acetylcholinesterase activity, appear to be more sensitive to O_3 exposure than pulmonary function tests or semiquantitative symptom evaluations. Significant ($P<.05$) losses in acetylcholinesterase activity and resistance of red cells to hemolysis were found in the total group of subjects exposed to 0.2 ppm, in whom symptom and pulmonary-function changes were not significant.

The overall results indicate that two-hour ozone exposures near the first-stage health advisory level result, at least among some population groups with respiratory hypersensitivity, in significant disturbances of blood biochemical function and in exacerbation of respiratory symptoms in certain individuals. Two-hour exposures at the second-stage alert level result in more severe effects, sufficient to incapacitate the most sensitive individuals during exposure and for several hours afterward. Some asthmatics and most individuals with respiratory hyperreactivity but without asthma suffer little apparent clinical effect at the latter exposure level, however.

* Ozone concentrations given throughout this report are based on the neutral buffered potassium iodide calibration method, and thus are discussed in relation to alert levels based on the same calibration method--0.20 ppm first stage and 0.40 ppm second stage.

RECOMMENDATIONS

The results of this study indicate that a comprehensive reevaluation of the first- and second-stage oxidant alert levels is needed. Ozone concentrations below the present first-stage health advisory level appear to be capable of producing deleterious acute effects in at least a few individuals,and many more people would be expected to experience ill effects at concentrations approaching the second-stage alert level. While improved control measures may reduce ambient oxidant levels significantly, there appears to be little hope of preventing relatively frequent and widespread occurrence of concentrations of 0.2 ppm and higher in the foreseeable future. We thus assume that despite control measures, prevailing oxidant concentrations probably will continue to exceed safe limits for some population groups. These people would need to be identified and assisted to take protective measures. Specific recommended approaches to this problem follow:

1. The relevance of the results of the present study to actual health effects of ambient exposure should be assessed. Specifically, health effects of well-characterized ambient oxidant exposures should be determined in volunteer subjects and compared in the same subjects with effects of controlled laboratory ozone exposures, in order to learn whether ambient oxidant mixtures differ substantially in toxicity from ozone alone. If so, appropriate adjustments of oxidant standards would be warranted.

2. More volunteer subjects should be studied in controlled ozone exposures in order to predict more accurately the incidence of adverse health effects at a given concentration. Special attention should be given to groups expected to show increased sensitivity, including (but not necessarily limited to) the following:

   a. Asthmatics. The results of this study predict a much increased incidence of respiratory disturbances in asthmatics as compared to normals at realistic ambient O_3 concentrations, but the sample studied was very small and did not include severe asthmatics, thus the results cannot be generalized reliably.

   b. Chronic bronchitis and emphysema patients. These individuals share some clinical characteristics with asthmatics, thus may also be hyperreactive to ozone. Furthermore, they exhibit marked shifts in ventilation distribution away from diseased lung tissue producing increased ventilation of relatively healthy areas of their lungs, which thus may receive inordinately high pollutant doses during ambient exposures.

   c. Cardiac disease patients. These individuals have impaired ability to deliver oxygen to body tissues and often have abnormally large amounts of extravascular lung fluid which may compromise pulmonary function, thus they may be highly sensitive to the additional respiratory insult of oxidant exposure.

d. Patients with glucose-6-phosphate dehydrogenase deficiency. This inherited trait is present in 10 percent or more of black Americans and is also found in many other ethnic groups of African or Asian origin. A variety of toxic exposures are known to produce hemolytic anemia episodes in deficient individuals; whether ambient oxidant exposures can do so is not known but may be suspected in light of the decreased resistance to hemolysis exhibited by red cells of ozone-exposed normal subjects.

3. Further studies should be conducted to compare monitoring-station data with actual oxidant doses received by representative members of the public (as determined by monitoring their immediate air environments), in order to evaluate the reliability of monitoring-station data and to determine the efficacy of various protective measures taken by individuals, e.g., remaining indoors when oxidant levels are high.

In summary, this study provides evidence that the current California first-stage health advisory and second-stage alert levels probably fail to protect significant numbers of individuals from adverse health effects of oxidant exposure. If more comprehensive studies corroborate these findings, the standards should be revised downward. Revision of standards would have substantial political and economic impact and thus cannot be recommended with finality solely on the basis of the relatively small amount of evidence now available. In addition to possible revision of standards, more effort should be directed toward identifying high-risk individuals and encouraging and assisting them to protect themselves from exposure.

INTRODUCTION

Ozone (O_3) has been of concern for more than twenty years as a potentially hazardous component of air pollution. Some animal toxicology studies of O_3[1] have shown detectable adverse effects at concentrations well within the range experienced during photochemical oxidant pollution episodes in California urban areas, particularly the South Coast Air Basin. Exposures to ambient oxidant mixtures, of which O_3 is the major component, have been associated with increased acute respiratory symptoms in healthy young adults,[2,3] impairment of athletic performance,[4] and increased asthmatic attacks in susceptible patients.[5] Studies designed to detect increased prevalence of chronic respiratory disease attributable to repeated photochemical oxidant exposures have thus far failed to detect such an effect, however.[6-8]

Previous studies in this laboratory[9-13] (CARB Contract No. 2-372) investigated the effects of controlled exposures to O_3 in highly purified air with secondary stresses--heat and light intermittent exercise--typical of those present in ambient oxidant exposures. In a small group of volunteer subjects, mostly young to middle-aged men in normal health, no significant health effects were detected in exposures to 0.25 ppm O_3, but blood biochemical, clinical, and respiratory physiological changes were detectable at 0.37 ppm and more pronounced at 0.50 ppm, although some individuals remained free of symptoms and pulmonary mechanical changes even after 5-6 hours at the highest concentration. The most reactive subjects in this study had histories of either mild asthma, respiratory allergies, or unusually high sensitivity (in their own judgment) to ambient smog exposures. This finding led to the hypothesis which is the subject of the present study--that asthmatics and other respiratory-hyperreactive individuals are more sensitive to O_3 challenge than normals, and thus require more careful protection from ambient exposures. This hypothesis was tested by exposing volunteer subjects with respiratory hypersensitivity or asthma to O_3 under simulated ambient exposure conditions as had been done with "normal" subjects. Certain modifications to the test protocol, described in the next section (Test Protocol), were introduced to deal more adequately with potential complications presented by asthmatic subjects. For safety and ethical reasons, mild hyperreactives were studied first, followed by mild to moderate asthmatics as more experience was gained. A parallel study was conducted to compare results from this laboratory with those from Canadian laboratories engaged in similar investigations;[14-17] many of its results are relevant to the current contract and thus are included in this report.

EXPERIMENTAL METHODS AND RATIONALE

Test Protocol

The exposure facility and basic experimental protocol, designed to simulate ambient oxidant exposures realistically, have been described in detail previously.[9-11] In general, three subjects were studied at a time, undergoing baseline function testing in the exposure chamber under clean-air conditions, then being exposed to O_3 for two hours, during which exercise at a work load of 150-200 kg-m/min was performed for the first 15 min in every 30. Exercise load was decreased in a few cases to keep the subjects' exercise heart rates below 140/min. Exposure temperature was 31°C (88°F) and relative humidity was 35% ± 4%. At the conclusion of the two-hour period, pulmonary testing was repeated; the exposure continuing during the testing. After pulmonary testing, exposure was stopped and the subjects were examined and interviewed by the project physician, who also drew venous blood for biochemical analysis. The same protocol was repeated on three successive days, the first of which was a sham-control (exposure to purified air only), the second an odor-sham control (brief low level O_3 exposure to allow perception of the odor, followed by purified-air exposure), and the third the actual exposure day.

The above-described protocol represents a modification of that used for normal subjects, intended to minimize problems expected in testing asthmatics. Asthmatics were expected to show more hour-to-hour and day-to-day variability in pulmonary function tests than normals, thus daily baseline measurements were needed. Pulmonary function in asthmatics was also expected to be influenced by psychological factors, possibly including anxiety at perceiving the odor of O_3 during exposure, thus the odor-sham control study was added to the protocol. These efforts to increase reliability of measurements also increased time and effort required of the subjects, however, and in some cases time constraints necessitated eliminating the odor-sham study day or the pre-exposure pulmonary testing. Retrospective examination of the data for subjects receiving both a sham and an odor-sham exposure revealed no significant differences in symptoms or pulmonary function between the two conditions. In most subjects tested, day-to-day variability in pulmonary function measures was small, as was pre- vs. post-exposure variability on control days, so there was no clear advantage in daily pre-exposure measurements. Some asthmatics, however, showed impairment of function after sham exposure, presumably induced by exercise and/or heat stress. Pre-exposure measurements also varied from day to day in some of these subjects, necessitating examination of measurements both between days and within days in evaluating whether changes attributable to O_3 took place.

Ozone Measurement

Under the preceding California Air Resources Board Contract No. 2-372, the primary O_3 monitoring instrument (REM chemiluminescent analyzer) was calibrated using 1% neutral phosphate-buffered potassium iodide solution and ozonized air of 35% - 50% relative humidity for the manual reference analysis. During this time, CARB established successive alert levels of 0.20, 0.40, and 0.60 ppm O_3 or oxidant, based on a very similar neutral buffered KI calibration method. A Dasibi ultraviolet photometric O_3 monitor factory calibrated according to the CARB method (calibration setting 68.6) was later acquired and found to give readings similar to those of the REM instrument. When a discrepancy among calibration techniques was later publicized,[18] it was decided to continue monitoring in the same manner for consistency with the previous health effects studies. Thus, O_3 concentrations given here may be directly related to ambient monitoring data obtained through 1974 outside Los Angeles County, but should be multiplied by 0.8 to compare with readings obtained by the current standard ultraviolet photometer method.

Selection of Subjects and Ozone Exposure Levels

Subjects were recruited for the study from the project staff, other hospital employees, and outside patient groups by self-referral or physician referral. Individual characteristics are given in Table 1. Informed consent was obtained from each subject before he or she was tested. Criteria for admission to the study were history of probable clinical respiratory hyperreactivity, either to smog or to other challenges such as allergens, and general health sufficiently good so that undergoing the testing did not present a substantial hazard. While evaluation of O_3 response in asthmatics was of major interest, subject safety considerations dictated that studies begin with subjects only mildly hyperreactive, since relatively severe reactions had been found previously (California Air Resources Board, Contract No. 2-372) in some hyperreactive individuals. After experience had been gained with mild hyperreactors, subjects with mild to moderate clinical asthma were studied. Exposure concentration initially chosen was 0.40 ppm O_3 -- the second-stage alert level and not substantially different from the nominal 0.37 ppm level previously found to produce no more than mild exposure effects in normals. Since one moderately asthmatic subject experienced a severe reaction to 0.40 ppm exposure, asthmatics studied subsequently were exposed only to 0.20-0.25 ppm for safety. A subsample of subjects exposed to 0.4 ppm were also exposed to 0.2 ppm in order to compare responses at the two concentrations. Individual exposure conditions are given in Table 2.

Data Analysis

Since individual responses to exposure were variable, data for each individual were examined separately for evidence of deleterious health effects of O_3 exposure. Since three values for each pulmonary-function measure were generally available under each experimental condition, t tests were applied to test for significant function differences between post-exposure and control conditions. Small statistically significant function changes were expected to be found occasionally due to chance (since many statistical comparisons were made) or due to normal day-to-day variability of function, thus statistical changes in individuals were considered "significant health effects" only when accompanied by increased symptoms or other corroborating evidence. For symptom and biochemical measures, only one measurement could be obtained for each subject and test condition, thus only group comparisons were made.

Group data for pulmonary-function measures, biochemical measures, and symptom score were compared between O_3 exposure and the immediately preceding control condition by paired statistical tests using each individual as his own control. The dependent t test was employed with physiological and biochemical data. The Wilcoxon signed-rank test was used with symptom-score data since the latter were semiquantitative in nature and not expected to be normally distributed. Groups compared consisted of all subjects exposed at a given concentration, and subgroups separated according to clinical criteria. Subjects were initially classified as "hyperreactors" (reporting smog sensitivity or respiratory allergy but denying asthmatic symptoms), "rare asthmatics" (reporting a history of rare wheezing episodes but not under treatment for asthma), and "clinical asthmatics" (reporting repeated wheezing episodes in the recent past and presently or previously on bronchodilator therapy). Test results suggested that clinical asthmatics differed substantially from the other two groups, but showed no obvious distinction between hyperreactors and rare asthmatics. Rare asthmatics were therefore included in the hyperreactor group for data analysis purposes in order to improve the sample size.

Group statistical analyses were limited to those measures which had been previously shown to be sensitive to O_3 effects (relative to their normal variability) and for which dose-response relationships had been demonstrated in the O3 concentration range of interest. These included red cell fragility (RBC F),red cell acetylcholinesterase activity(AC), one-second forced expiratory volume (FEV_1), delta nitrogen (ΔN_2), and symptom score (SS).

Investigation of Ozone Adaptation (Related Study)

This study was supported by Grant No. HL 15098, National Heart and Lung Institute. To determine whether Los Angeles area residents were less reactive to O_3 than nonresidents, a relatively homogeneous group of volunteer subjects, some of whom were Los Angeles residents and some of whom were nonresidents, was exposed to 0.4 ppm O_3 using a protocol similar to that described previously. Subjects were recruited from the incoming class of the University of Southern California School of Physical Therapy -- a young, healthy adult group approximately evenly divided between residents and nonresidents. Nonresidents were studied within five days of their arrival in Los Angeles and were instructed to minimize intercurrent ambient oxidant exposures by remaining indoors or in coastal areas during smog episodes. Studies were conducted in September 1975,i.e., near the end of the Los Angeles summer smog season, when residents should have had ample opportunity to develop adaptation to ambient oxidant exposure, if such existed. Subjects underwent a sham exposure on one day and an O_3 exposure on the following day. Post-exposure test results were compared between the two days. Reactivity of each individual was expressed in terms of change in FEV_1 and change in symptom score, and statistical tests were applied to test for differences in mean reactivity between residents and nonresidents.

RESULTS

Group Responses

Mean responses of biochemical, physiological, and symptom indices in groups exposed to approximately 0.4 and approximately 0.2 ppm O_3 are given in Table 3. Responses are expressed in terms of the change in the post-exposure measurement from the last preceding control measurement.

At 0.4 ppm, pulmonary physiological changes occurred as reflected by significant loss in FEV_1 and increase in delta N_2. These changes were relatively slight, i.e., not much greater than the normal test-to-test variability of the measurements. Individual changes tended to be largest in clinical asthmatics and in non- Los Angeles residents, who also tended to have more exposure-related symptoms. For the entire 0.4 ppm group, however, only a small correlation was found between increased symptom score and decreased FEV_1 (Spearman rank correlation coefficient = .21). Group changes in symptom score (SS) and red cell acetylcholinesterase activity (AC) were more highly significant than physiological changes. Analogous changes were found previously in a group of normal subjects exposed to 0.37 ppm, in whom no significant changes in delta N_2 and FEV_1 were found. A trend toward increased red-cell fragility (RBC F), i.e., decreased resistance to hemolysis when exposed to H_2O_2 *in vitro*, did not attain statistical significance. Reduction in AC was the most consistent finding. Changes in AC were similar in asthmatics and non-asthmatics, whereas other effects were usually more pronounced in asthmatics.

The group exposed to 0.2 ppm had a higher proportion of asthmatics, and so might be considered more reactive on the average than the group exposed to 0.4 ppm. At 0.2 ppm, no significant group changes in FEV_1, ΔN_2 or SS were found. Acetylcholinesterase activity was significantly reduced, the mean percent change from control being slightly less than half as large as in the 0.4 ppm group. Red-cell fragility was also significantly increased in the 0.2 ppm group.

Individual Responses

Individual responses are given in Tables 4-6. The most reactive individuals are discussed in the text following.

Subject 48 (male, age 33) had had asthma since childhood but had refrained from using bronchodilator medication by his own choice since age 21. He had never smoked regularly. His baseline pulmonary tests showed an elevated closing volume and mildly reduced FEV_1. He was essentially asymptomatic during the sham study. No odor-sham study was done due to time limitations. During exposure to O_3 at 0.37 ppm, he

developed productive cough, wheezing, chest restriction, substernal irritation, reduced FVC and FEV_1, and increased delta N_2. The decrement in FVC and FEV_1 was partially reversed in seven hours and fully reversed by 24 hours after exposure. He reported that cough persisted for one day following exposure and that wheezing episodes were more frequent than usual for 4-5 days following exposure.

Subject 61 (male, age 50) had had asthma since childhood, used oral and inhaled bronchodilators, and had been a moderate smoker but had quit at age 40. His baseline pulmonary tests showed reduced FEV_1 but normal closing volume and delta N_2. He was a resident of metropolitan San Diego, thus probably had received less ambient oxidant exposure than the other Southern California subjects, all of whom were Los Angeles area residents. During both sham and odor-sham studies he developed wheezing, chest restriction, dyspnea, and reduction in FVC and FEV_1. When exposed to 0.25 ppm O_3, he developed symptoms more severe than on the control days and larger relative changes in forced-expiratory function measures. (Table 7.) However, his baseline function measures on the exposure day were also worse than on the control days.

Subject 62 (female, age 57) had adult-onset asthma and chronic productive cough. She had never smoked regularly. Her baseline FVC and FEV_1 were reduced and delta N_2 was elevated. She was on oral and inhaled bronchodilator medication. She experienced cough, wheezing, chest restriction, dyspnea, reduced FVC and FEV_1, and increased delta N_2 both during control studies and during 0.25 ppm O_3 exposure. Clinical and physiological changes were not increased with O_3 as compared to control (Table 7), but on unusually large increase in RBCF occurred with O_3 exposure (Table 6).

Subject 63 (female, age 28) had had asthma since childhood and used inhaled bronchodilators occasionally. She had been a light smoker during her late teens but had quit thereafter. Her baseline pulmonary function tests were all well within normal limits. She experienced some lower-respiratory symptoms during both control studies, but pulmonary function measures remained stable or improved slightly. During 0.25 ppm O_3 exposure she developed small but significant losses in FVC and FEV_1 (Table 7) and increased chest restriction and substernal irritation relative to control days.

Subject 64 (male, age 38) had no history of wheezing but had a long history of upper-respiratory allergy. His baseline pulmonary function tests were normal. He had been a light smoker briefly but had quite at age 23. He was essentially asymptomatic and stable in pulmonary-function measures during sham and odor-sham studies. During exposure to 0.35 ppm O_3, he developed chest restriction, substernal irritation, nasal congestion, headache, reduced FVC, and marginally reduced FEV_1. The symptoms persisted several hours following exposure.

Subject 43 (male, age 29) had had asthma since childhood, used inhaled bronchodilators occasionally, and had never smoked regularly. His baseline FVC was unusually large, causing his FEV_1/FVC ratio to be below normal, although FEV_1 itself was within normal limits. Delta nitrogen was normal. In sham and odor-sham studies he showed slight losses in FVC. Exposure to 0.41 ppm O_3 produced a greater loss in FVC, substernal irritation, and chest restriction. Only marginal changes in FEV_1 were seen.

Subjects 19 (male, age 39) and 20 (female, age 33) were residents of Ontario, Canada. Neither had history of asthma or respiratory allergy but both had been found unusually reactive to O_3 at higher concentrations in previous Canadian studies. When exposed to 0.37 ppm O_3, both developed cough, substernal irritation, chest restriction, markedly reduced FVC and FEV_1, and increased delta N_2.

Reactivity to Ozone in Relation to Clinical Characteristics

Data from present and previous ozone exposure studies in this laboratory were examined in relation to the hypothesis that asthmatics or other clinically hyperreactive individuals are more reactive to ozone than normals. Information was not available for calculation of comparative dose-response curves for different clinically-defined groups, since experimental conditions were not uniform throughout all studies. The entire subject group was dichotomized into "reactive" and "non-reactive" groups on the basis of responses to ozone and the prevalence of "reactivity" examined in clinically definable groups. "Reactivity" to ozone was defined as statistically significant loss in FVC and/or FEV_1 plus increase in symptom score of at least four ss units* upon exposure to 0.40 ppm or less for two hours with intermittent exercise. Subjects without both symptom and function changes were considered "non-reactive" although they may have shown biochemical changes. Four subjects could not be classified since they were found "non-reactive", but were not tested at concentrations as high as 0.4 ppm with exercise. Non-Southern California residents were excluded from consideration since they were suspected to be more reactive due to lack of adaptation. Classifiable subjects were divided clinically into 9 normals, 14 hyperreactors (including "rare asthmatics" as described previously), and 5 clinical asthmatics. No normals were reactive to ozone by the above criteria, but 2 hyperreactors and 4 asthmatics were reactive. Both chi-square tests and an exact-probability calculation (more reliable with small sample sizes) indicated a significantly ($P < .01$) increased prevalence of "reactivity" in asthmatics (Table 8). While this finding is highly suggestive, it should not be taken as conclusive evidence that Southern California asthmatics in general are more likely to be ozone-reactive than normals, since the sample total was small and the definitions of reactivity and clinical status are necessarily somewhat arbitrary.

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* The choice of a particular symptom score increase as representing meaningful "clinical reactivity" is necessarily arbitrary since the scores are subjective and not strictly quantitative. The choice of four as the critical score (expressed as exposure score minus control score) is based on the following criteria: (a) Any single "incapacitating" symptom experienced during exposure but not during control study gives a score increase of 4. (b) Milder exposure-related symptoms give smaller score increases, but since multiple symptoms are likely to result from exposure and some redundancy is present in the interview questions, a genuinely O_3-related response is likely to result in a score increase of 4 or more. (c) Score increases as large as 4 under non-exposure conditions are uncommon. In 18 subjects receiving successive sham and odor-sham exposures, the mean change in ss was +0.5 (not significant by t or Wilcoxon test), standard deviation was 2.6 and range was -3 to +7.5. Two subjects (11%) had ss increases as large as 4.

Reactivity in Los Angeles Residents vs. Nonresidents

This study is not part of the current contract and data have not been fully evaluated, so only a summary of preliminary results is given here. Six Los Angeles area residents and nine nonresidents were exposed to 0.4 ppm O_3 for two hours with intermittent light exercise at 31°C and 35 percent relative humidity. Two nonresidents were male; all other subjects were female. No sex differences in response were apparent in this group or in previous studies. Some subjects had a history of allergy, but none had history of asthma or wheezing. Individual reactivity was assessed in terms of change in FEV_1 and symptom score. Three nonresidents were judged "reactive" by the criteria given in the preceding section; three others showed significant losses in FEV_1 without substantially increased symptoms. No residents were "reactive" but two showed FEV_1 losses. Group symptom-score data were analyzed by Wilcoxon and Mann-Whitney tests. Mean change in symptom score between control and exposure was +2.7 for nonresidents and +0.6 for residents. Differences between groups and between control and exposure conditions were not significant. Group FEV_1 data were analyzed by t tests. Nonresidents showed a loss in FEV_1 of 4.6 percent ± 5.3 percent (mean ± standard deviation); this change was significant ($P = .02$, one-tailed test). Residents showed a non-significant loss in FEV_1 of 0.5 percent ± 2.9 percent. The difference in mean FEV_1 loss between nonresidents and residents did not achieve statistical significance according to the t test (one-tail $P = .06$), but a significant difference was shown when the Mann-Whitney test was applied to the same data (one-tail $P = .03$). The nonparametric Mann-Whitney test may be more appropriate in this case since distribution of responses is expected to be, and in fact appears to be, non-normal--skewed strongly in the negative direction by the responses of a few highly reactive subjects. The individual control-vs.-exposure FEV_1 data were also reexamined by a non-parametric test (Wilcoxon), which showed a higher level of significance ($P < .005$) for the mean FEV_1 change in nonresidents than had the t test, and again showed non-significance for the mean FEV_1 change in residents.

These results provide further support for the hypothesis that at least some Los Angeles area residents develop adaptation to O_3 exposure. The observed difference in mean FEV_1 response between residents and nonresidents is reasonably similar to differences previously observed between Los Angeles and Canadian subject groups.

TABLE 1

SUBJECT CHARACTERISTICS

SUBJECT NO.	SEX	AGE	HT.,CM	WT.,KG.	SMOKING(a)	CLINICAL CHARACTERISTICS(b)	REMARKS
2	M	57	183	81	-	E	
5	M	57	170	68	-	D,E	
7	M	38	175	73	-	C,D,E	
9	M	43	183	91	former (10)	C,D,E	
10	M	31	173	78	current (36)	A,D,E	
11	M	30	180	70	-	F	
16	M	32	178	70	current (9)	F	
19	M	39	185	91	-	F	(c)
20	F	33	160	63	current (d)	F	(c)
21	M	35	175	96	current (18)	D	(c)
22	F	32	160	58	current (7)	D	(c)
23	F	23	160	49	current (9)	E	
24	M	56	178	77	-	C,D,E	
25	M	29	185	77	former (3)	C,D,E	
41	M	21	185	81	-	E	
42	M	24	178	73	current (14)	B,D	
43	M	29	193	85	-	A,D	
44	F	28	150	85	-	-	(e)
45	F	64	163	54	-	-	(e)
46	M	55	173	66	former (10)	-	(e)
48	M	33	193	107	-	A,D,E	
61	M	50	175	68	former (20)	A,B,D	(f)
62	F	57	168	68	-	A,B,D	
63	F	28	165	54	former (3)	A,D	
64	M	38	180	86	former (1)	D,E	

TABLE 1 (continued)

NOTES: (a) All smokers smoked cigarettes only; estimated lifetime dose in pack-years (average packs/day times years smoked) given in parentheses.

(b) Clinical characteristics coded as follows:

A = clinical asthma, B = persistent cough, C = history of rare wheezing episodes ("rare asthmatic"), D = respiratory allergy, E = subjective sensitivity to ambient oxidant exposure, F = previously observed unusual reactivity in controlled O_3 exposure at 0.5 ppm (subjective response plus physiological changes).

(c) Resident of Canada.

(d) Smokes no more than one cigarette/day.

(e) These subjects were identified as having mild pulmonary function abnormalities in on industrial screening study, but showed no significant clinical abnormalities on examination. They were exposed to 0.4 ppm O_3 at rest, since subject 44 developed exercise tachycardia. None showed significant exposure effects. Since their exposure conditions did not conform to the usual protocol, they were not included in group data analyses.

(f) Resident of San Diego area.

TABLE 2

OZONE EXPOSURE CHARACTERISTICS

GROUP NO.	PPM OZONE, MEAN±S.D. REM MONITOR	DASIBI MONITOR	CONTROLS(a)	SUBJECTS
8	.37±.02	-	A	19,20,21,22
9	.38±.02	-	A	7,11,16,23
11	.36±.04	-	A,B,C	7,10,11
12	.34±.07	-	A,B,C	24,25
17	.38±.08	.40±.10	A,B,C	2,5,41
18	.22±.08	.23±.08	A,B,C	10,24,25
19	.20±.02	.20±.01	A,B,C	7,9,16
20	.41±.04	.37±.04	A,B,C	42,43
21 (b)	.42±.02	.39±.02	B,C	44,45,46
22	.37±.08	.36±.08	A	48
29	.26±.02	.25±.02	A,B,C	61,62,63
30	.22±.04	.24±.04	C	19
31	.35±.04	.38±.05	A,C	23,24,64

NOTES: (a) Control conditions coded as follows:

A = sham exposure study, B = odor-sham exposure study (<0.10 ppm O_3 for <10 min, followed by sham exposure), C = daily pre-exposure physiological measurements.

(b) Subjects not exercised. See Table 1, note (e).

TABLE 3

MEAN EFFECTS OBSERVED IN SUBJECT GROUPS EXPOSED TO O_3 FOR 2 HOURS WITH INTERMITTENT EXERCISE

GROUP (NO. OF SUBJECTS)	MEAN CHANGE EXPOSURE VS. CONTROL (a) SS	FEV_1	FEV_1(b)	ΔN_2	ΔN_2(b)	AC	RBCF
0.37 - 0.41 ppm O_3							
Asthmatics + Hyperreactors (18)	+7.2 <.005	-3.1 <.005	-2.1 .04	+20 .01	+22 .01	-6.4 <.005	+6.0 NS
Hyperreactors (15)	+5.3 <.005	- 2.3 .03	-1.8 NS	+19 .04	+21 .03	-6.8(c) <.005	+7.2(c) NS
Asthmatics (3)	+16.5 NS	-7.7 NS	-3.4 NS	+27 .03	+33 NS	-4.9 .04	+0.3(c) NS
Hyperreactors, Los Angeles Residents only (11)	+4.0 .01	-1.2 .02	-0.4 NS	+13 NS	+13 NS	-5.0 <.005	-0.9 NS
0.20 - 0.25 ppm O_3							
Asthmatics + Hyperreactors (10)	+0.7 NS	-0.8 NS	-3.6 NS	-10 NS	+5 NS	-2.7 .02	+13.8 .02
Hyperreactors (6)	-0.8 NS	+2.4(c) NS	+3.0 NS	+12(c) NS	-9 NS	-2.9 .03	+10.3 NS
Asthmatics (4)	+3.0 NS	-6.6 NS	-13.5 NS	-15 NS	+25 NS	-2.4 NS	+19.8 NS

NOTES: (a) Change in post-O_3 exposure measurement from post-exposure measurement on immediately preceding sham-exposure day, except where indicated otherwise. P value describing statistical significance given immediately below each entry. SS given as absolute change with P by Wilcoxon test; others given as percent change with P by paired t test. Probability is for one tail in each case.

(b) Percent change from last preceding control measurement (pre-O_3 exposure baseline except when not available, in which case previous day post-sham exposure value is used). As can be seen, mean FEV_1 changes are often smaller when expressed in this manner.

(c) No data for one subject.

TABLE 4

INDIVIDUAL SYMPTOM SCORES--EXPOSURE DAY VS. LAST CONTROL DAY (a)

SUBJECT	NOMINAL EXPOSURE (O_3)	SCORE CONT.	SCORE EXP.	SUBJECT	NOMINAL EXPOSURE (O_3)	SCORE CONT.	SCORE EXP.
2	.4	0	0	24	.4	1	10.5
5	.4	1.5	2	24	.2	0	0
7	.4	0	1.5	25	.4	3.5	6
7	.2	1.5	0	25	.2	9.5	11.5
9	.2	10	2.5	41	.4	2	6
10	.4	9	12	42	.4	5.5	4.5
10	.2	6.5	10.5	43	.4	0.5	6
11	.4	1	0.5	44	.4(b)	3	4.5
16	.4	0.5	1.5	45	.4(b)	4.5	0
16	.2	0	0	46	.4(b)	3	5
19	.4	1.5	20	48	.4	1	42
20	.4	3	9	61	.2	21	31
21	.4	0	7	62	.2	30	17.5
22	.4	3.5	8	63	.2	18.5	29
23	.4	4	10.5	64	.4	1	21

NOTES: (a) Symptoms scored: Cough, sputum, substernal irritation, chest restriction, nasal discharge, laryngitis, dyspnea, wheezing, headache, fatigue. Each symptom scored for each of 3 periods: During exposure, after exposure, morning of following day. Scoring: Minimal = 0.5 unit, mild = 1, moderate = 2, severe = 3, incapacitating = 4.

(b) Exposed at rest.

TABLE 5A

INDIVIDUAL SPIROMETRIC RESULTS--EXPOSURE DAY VS. LAST CONTROL DAY

SUBJECT	NOMINAL EXPOSIRE (O_3)	FVC(a)		FEV_1(b)		MMF(c)	
		CONT.	EXP.	CONT.	EXP.	CONT.	EXP.
2	.4	6.07	6.13	4.69	4.55	3.97	3.87
5	.4	4.19	3.97	3.09	3.07	2.41	2.87
7	.4	4.82	4.73	3.82	3.70	4.0(d)	4.1(d)
7	.2	5.17	5.14	3.81	3.86	2.78	2.94
9	.2	6.26	6.26	5.08	5.19	5.13	4.79
10	.4	4.12	4.08	2.89	2.80	2.5(d)	2.2(d)
10	.2	4.30	4.40	3.16	3.28	2.39	2.27
11	.4	4.31	4.30	3.85	3.84	5.7(d)	5.7(d)
16	.4	5.35	5.56	4.36	4.34	5.4(d)	4.8(d)
16	.2	5.36	5.36	4.27	4.37	3.96	4.31
19	.4	6.07	4.90	4.81	4.20	6.0(d)	3.2(d)
19	.2	5.79	5.77	4.52	4.50	4.72	4.48
20	.4	3.26	3.00	2.54	2.25	2.7(d)	2.1(d)
21	.4	5.05	5.25	4.20	4.26	5.7(d)	6.1(d)
22	.4	3.82	3.99	3.37	3.35	4.2(d)	4.0(d)
23	.4	3.72	3.79	2.85	2.93	3.1(d)	2.6(d)
24	.4	4.47	4.30	3.44	3.35	3.17	2.99
24	.2	4.34	4.27	3.28	3.25	2.67	2.60
25	.4	6.18	6.24	4.87	4.75	4.38	4.08
25	.2	6.27	6.27	4.72	5.00	3.80	4.64
41	.4	5.35	5.32	4.77	4.78	6.04	5.79

TABLE 5A (continued)

SUBJECT	NOMINAL EXPOSURE (O_3)	FVC(a) CONT.	FVC(a) EXP.	FEV_1(b) CONT.	FEV_1(b) EXP.	MMF(c) CONT.	MMF(c) EXP.
42	.4	5.51	5.46	4.32	4.27	3.97	3.74
43(e)	.4	6.67	6.44	4.24	3.81	2.49	2.14
44	.4(f)	3.09	3.12	2.38	2.34	2.09	1.97
45	.4(f)	3.47	3.41	2.61	2.55	1.95	2.08
46	.4(f)	4.02	3.84	2.53	2.47	0.97	1.08
48	.4	5.25	5.00	3.35	3.06	1.70	1.49
61(e)	.2	5.36	4.37	3.34	2.25	1.78	0.98
62(e)	.2	2.12	2.47	1.23	1.50	0.52	0.57
63(e)	.2	4.40	4.20	3.71	3.65	4.00	4.33
64	.4	5.73	5.50	4.63	4.56	4.61	5.08

NOTES:

(a) In liters. Best of $\geq$ 3 efforts.

(b) In liters. Best of $\geq$ 3 efforts, not necessarily from same trial as best FVC.

(c) In liters/sec. From trial with best FVC.

(d) $\dot{V}_{50}$ measured instead of MMF.

(e) Asthmatic subject showing pre-vs. post-sham exposure function decrement. See Table 7 for detailed results.

(f) Exposed at rest.

TABLE 5B

INDIVIDUAL SINGLE-BREATH NITROGEN TEST RESULTS--
EXPOSURE DAY VS. LAST CONTROL DAY (a)

SUBJECT	NOMINAL EXPOSURE (O_3)	CV/VC(%)		CC/TLC(%)		ΔN_2	
		CONT.	EXP.	CONT.	EXP.	CONT.	EXP.
2	.4	15.8	14.1	35.3	36.3	0.40	0.40
5	.4	16.2	16.7	37.4	38.1	0.40	0.43
7	.4	18.9	16.7	37.2	34.7	0.66	0.87
7	.2	13.7	12.9	27.8	27.2	0.57	0.47
9	.2	9.7	11.1	26.4	27.1	0.40	0.53
10	.4	11.4	9.3	33.7	31.5	1.47	1.67
10	.2	8.4	10.8	28.9	29.8	1.42	1.23
11	.4	4.4	2.7	21.8	22.9	0.80	0.93
16	.4	11.8	9.2	27.2	25.1	0.60	0.63
16	.2	8.7	9.4	19.3	18.9	0.43	0.60
19	.4	12.6	10.9	30.9	33.4	0.53	1.25
19	.2	14.1	13.3	28.8	27.5	0.77	0.67
20	.4	8.6	8.3	29.2	33.1	1.67	2.33
21	.4	16.5	14.1	33.5	32.0	0.52	0.57
22	.4	2.8	7.1	28.5	30.3	1.63	1.43
23	.4	6.3	10.3	27.8	31.8	1.66	2.43
24	.4	16.1	13.8	36.6	36.0	1.07	0.97
24	.2	17.1	14.7	38.6	36.2	0.77	0.83
25	.4	5.6	7.8	24.8	25.0	0.70	0.87
25	.2	12.3	9.6	26.5	25.6	0.63	0.70
41	.4	4.9	2.3	22.6	21.2	0.73	0.70
42	.4	7.9	13.4	18.2	26.0	0.87	0.77

TABLE 5B (continued)

SUBJECT	NOMINAL EXPOSURE (O_3)	CV/VC(%) CONT.	CV/VC(%) EXP.	CC/TLC(%) CONT.	CC/TLC(%) EXP.	ΔN_2 CONT.	ΔN_2 EXP.
43	.4	3.8	1.9	25.9	26.3	0.73	0.97
44	.4(b)	4.5	2.8	22.0	18.0	0.63	0.73
45	.4(b)	27.0	23.7	43.3	42.5	2.17	1.57
46	.4(b)	18.1	16.2	39.1	37.8	2.43	2.33
48	.4	25.7	19.4	43.3	40.8	1.06	1.50
61	.2	0	1.7	28.1	43.4	0.60	1.23
62	.2	(c)	(c)	(c)	(c)	7.00	5.10
63	.2	3.5	2.2	26.8	18.3	1.13	1.03
64	.4	13.6	11.7	26.5	25.7	0.73	0.73

NOTES: (a) All values given are means of 3 measurements, except that CV/VC is mean of 3 CV measurements divided by best of 3 VC measurements. Delta N_2 units are N_2 concentration increase (in percent) per liter expired.

(b) Exposed at rest.

(c) Not measurable due to pulmonary function abnormality.

TABLE 6

INDIVIDUAL BLOOD BIOCHEMICAL RESULTS
EXPOSURE DAY VS. LAST CONTROL DAY

SUBJECT	EXPOSURE (O_3)	ACETYLCHOLINESTERASE (a)		RBC FRAGILITY (b)	
		SHAM	EXP.	SHAM	EXP.
2	.4	17.11	16.41	22.37	21.94
5	.4	21.17	20.29	20.47	21.66
7	.4	21.24	20.11	13.73	16.73
7	.2	18.74	18.57	25.00	25.20
9(c)	.2	21.17	20.82	25.03	24.70
10	.4	23.81	23.02	23.71	22.93
10	.2	22.62	21.96	17.91	17.51
11	.4	21.10	18.96	19.54	21.25
16	.4	19.71	18.26	22.80	15.87
16	.2	17.64	17.20	26.47	25.23
19	.4	20.77	18.17	14.20	21.92
19	.2(d)	20.86	20.37	19.60	25.97
20	.4	21.65	18.52	14.48	19.34
21	.4	24.03	22.27	16.74	24.86
22	.4	22.93	20.72	15.82	22.40
23	.4	22.05	20.33	18.26	16.21
24	.4	22.36	21.83	14.9	7.4
24	.2	21.83	20.11	18.84	23.93
25	.4	21.61	22.05	15.1	8.1
25	.2	23.51	23.15	23.18	27.40
42	.4	22.71	21.39	28.80	31.55

TABLE 6 (continued)

SUBJECT	NOMINAL EXPOSURE (O_3)	ACETYLCHOLINESTERASE (a)		RBC FRAGILITY (b)	
		SHAM	EXP.	SHAM	EXP.
43	.4	21.83	20.07	29.23	30.15
44	.4(e)	19.54	17.64	24.90	25.41
45	.4(e)	17.64	16.32	23.84	23.59
46	.4(e)	15.57	14.99	22.82	24.03
48	.4	21.74	20.99	(f)	
61	.2	21.17	20.29	23.73	27.31
62	.2	19.93	18.52	14.94	25.04
63	.2	18.43	19.40	21.63	23.85
64	.4	20.11	19.01	22.89	29.47

NOTES: (a) Units/g hemoglobin/min.

(b) Percent hemolysis in 2% hydrogen peroxide.

(c) Studied under previous contract, found clinically and physiologically reactive at 0.5 ppm but not at 0.37 ppm.

(d) Sham measurement made before exposure on same day.

(e) No exercise.

(f) Blood sample unsatisfactory.

TABLE 7

DETAILED INDIVIDUAL SPIROMETRIC RESULTS PRE- AND POST-EXPOSURE IN ASTHMATICS SHOWING CHANGES NOT ENTIRELY ATTRIBUTABLE TO O_3 EXPOSURE

SUBJECT	(O_3)	TEST	SHAM PRE	SHAM POST	ODOR-SHAM PRE	ODOR-SHAM POST	EXPOSURE PRE	EXPOSURE POST
43	.4	FVC	7.03	6.75*	6.88	6.67*	6.90	6.44*
		FEV_1	3.91	3.94	4.10	4.24	3.87	3.81
		MMF	1.81	2.27	2.09	2.49	2.01	2.14
61	.25	FVC	5.31	5.02*	5.34	5.36	5.09	4.37*
		FEV_1	3.68	3.11*	3.61	3.34*	3.00	2.25*
		MMF	1.96	1.73	2.45	1.78	1.58	0.98
62	.25	FVC	2.51	2.01*	2.62	2.12*	2.81	2.47*
		FEV_1	1.60	1.24*	1.70	1.23*	2.04	1.50*
		MMF	0.77	0.56	0.58	0.52	1.44	0.57
63	.25	FVC	4.10	4.33	4.27	4.40	4.33	4.20*
		FEV_1	3.74	3.73	3.58	3.71	3.78	3.65*
		MMF	4.58	4.24	3.57	4.00	4.48	4.33

*Comparison of repeated measured by t test showed significant decrease from pre-exposure values (one-tail $p<.05$). Values given represent best efforts.

TABLE 8

NUMBER OF SUBJECTS REACTIVE TO O_3 EXPOSURE
AT 0.4 ppm OR LESS, BY CLINICAL CLASSIFICATION (a)

GROUP	REACTIVE (b)	NONREACTIVE	X^2	P
Normal (c)	0/9	9/9		
Hyperreactive (d)	2/14	12/14		
Clinical Asthmatic (e)	4/5	1/5	13.07	<.01
Normal + Hyperreactive	2/23	21/23		
Clinical Asthmatic	4/5	1/5	12.40	<.01

(Exact probability of obtaining this or a more extreme distribution by chance = .0034)

NOTES: (a) Exposure for 2 hr with light exercise 15 min in every 30.

(b) Subjects considered reactive if a statistically significant loss occurred in FVC and/or FEV_1 between control and post-exposure measurements while at the same time symptom score increased by $\geq$ 4 units.

(c) Subjects with normal baseline pulmonary function who denied history of wheezing or smog sensitivity.

(d) Subjects never under treatment for asthma but with history of rare wheezing episodes, respiratory allergy, or subjective smog sensitivity. (Three additional subjects were studied but only with a lower exposure dose, thus were not included in the count.)

(e) Subjects reporting frequent wheezing episodes and presently or previously on bronchodilator therapy. (One additional subject studied at a lower dose not included in count.)

DISCUSSION

Abundant evidence now exists that O_3 in concentrations equal to or less than those attained in ambient air during photochemical pollution episodes can exert harmful effects on human health. State air-quality standards, enforceable by compulsory restrictions on polluting activity, have been established for protection of the public from these harmful effects. Economic and social costs of pollution control are substantial, however, necessitating some compromise between health benefits gained and costs incurred in control efforts. The strategy adopted to deal with this problem is a flexible response to pollution episodes, with increasingly stringent controls imposed in proportion to increasing risk to public health.* Thus in the first-stage response, only health warnings are issued, allowing highly susceptible groups and individuals to take protective measures with only slight effect on normal economic activity. Not until the second-stage O_3 concentration is exceeded, constituting a more serious health risk, are compulsory abatement procedures instituted. The results of this study tend to confirm the wisdom of the flexible-response strategy in that they support the hypothesis that a few people suffer harm at low levels which are experienced frequently, while the majority suffer detectable short-term effects only at somewhat higher concentrations experienced relatively infrequently (Fig. 1). A first-stage health advisory concentration may then reasonably be set to protect the most susceptible few and a second-stage concentration set to protect the majority. The present first- and second-stage concentrations (0.20 and 0.40 ppm**) may be inadequate protection, however, as discussed below.

Of subjects exposed to approximately 0.4 ppm in this laboratory, a significant minority have shown physiological and clinical effects sufficient to impair normal performance. A few have been incapacitated during exposure and for periods of hours after exposure. No"normal" Los Angeles resident (without history of respiratory disease, allergy, or subjective smog sensitivity) has been found to be thus affected; all those who showed high reactivity were non-Los Angeles residents or asthmatic or hyperreactive residents. Thus the second-stage alert level may not be adequate to protect the latter groups. Furthermore, the lack of response in "normals" at this level applies only to conditions of light intermittent exercise. Heavy exercise at the same concentration would substantially increase the effective dose of O_3 and might be expected to produce more marked responses.

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* California Air Pollution Emergency Plan, Revised October 21, 1975. Air Resources Board, Sacramento.

** These standards may have in effect been relaxed slightly by the change to the ultraviolet photometer calibration standard, since 0.20 ppm (UV) $\approx$ 0.24 ppm (KI method) and 0.35 ppm (UV) $\approx$ 0.44 ppm (KI).

Of subjects exposed to approximately 0.2 ppm, most have shown no detectable clinical or physiological effect, but two asthmatics have experienced exacerbation of symptoms and some physiological changes. How typical these responses are of asthmatics in general cannot be known without further studies. It would appear likely, however, that many asthmatics are significantly reactive to 0.2 ppm or less if two reactors can be found in a very small sample (subjects exposed to 0.2 ppm or less: 10 total, 4 asthmatics). Again, heavier exercise would tend to increase the likelihood of significant response. More severe responses also might be expected in individuals with more severe disease.

Consistent blood biochemical changes have been found in both the 0.2 ppm and 0.4 ppm exposure groups. These are difficult to correlate with clinical or other health effects and cannot unequivocally be called harmful, given their small magnitude. On the other hand, they give evidence of some disruption of red cells analogous to premature aging in these cells, and warrant concern, at least in individuals with preexisting impairments of red-cell function. In addition, the change in acetylcholinesterase activity is the most consistent and sensitive (in terms of statistical significance) of all tests used to detect O_3 expsoure effects, and shows the most consistent dose-response relationship.

The preponderance of evidence obtained suggests that substantial numbers of people may not be protected from adverse health effects by the current oxidant air-quality standards. Further research as outlined in the Recommendations Section is needed to confirm this, given the economic and political costs involved in revision of standards. Decisions regarding new air-quality health protection policies, if such are found to be required, depend on many non-health-related social factors beyond the scope of this study. The health-effects information by itself can, however, provide guidelines which should be followed by any air-quality standard and its accompanying implementation plan, regardless of other constraints. Some of these are as follows:

1. Exposures producing catastrophic health effects (serious illness, permanent disability, or death) in any individual must be prevented, regardless of economic or other social concerns.

2. Exposures producing relatively mild, reversible adverse health effects of exposure should be permitted only if economic or social costs of their prevention are excessive. (In other words, cost-benefit analyses are appropriate in determining to what extent short-term fully reversible effects may be permitted, while permanent adverse effects should never knowingly be permitted at all.)

3. Maintenance of safe ambient air quality is the most reliable way of preventing hazardous exposures and is thus the method of choice.

4. When safe ambient air quality cannot be maintained, individual protective action may be a satisfactory alternative. Requirements for individual protective action include the following:

a. Identification of people at risk. This requires accurate dose-response information for all population groups likely to be at risk in the exposure range of concern. Inadequate dose-response information may lead either to inadequate protection or to over-protection, either of which could be very high in economic and social costs.

b. Evaluation of alternative protective measures. These would include avoiding exercise, remaining indoors, use of air filters, etc. Cost-benefit analyses should be used to determine optimum protection strategies.

c. Provision for highly reliable warning and implementation procedures. Improvement in ability to predict oxidant episodes is of great importance in this regard, as is improved understanding of the problem on the part of the health-care professions, public officials, the news media, and the general public.

5. The second-stage or compulsory-abatement alert level should protect working people--in normal health or otherwise--from health effects sufficient to impair performance significantly. If control technology is inadequate to keep oxidant concentrations below the required level, provision should be made for compulsory work modification or other protective action.

6. The first-stage or health-warning alert level should protect the most sensitive group (presumably with pre-existing disease) from significant exacerbation of their condition. The level cannot be set so low that warnings are repeated so often as to be widely ignored, so if the alert level fails to protect extremely sensitive individuals, they should be provided "continuous protection" through use of air purifying equipment, change of residence, change of occupation, etc.

In conclusion, the major findings under this contract will be restated: Individuals with respiratory disease appear to be more at risk from ozone exposure than normals and to be inadequately protected by current air-quality standards. More study is required to confirm these findings and to assess the degree of risk to various population groups. Improved protective action directed at high-risk groups may be necessary unless and until a marked reduction in ambient oxidant concentrations is achieved.

Figure 1. Prevalence of Elevated Ambient Oxidant Concentrations in Selected California Cities, Related to Air-Quality Standards and Health-Effects Information.

Explanation: Lines represent frequency distributions of daily maximum hourly average oxidant readings (one-hour averaging time, all readings converted to neutral buffered KI calibration method) at the indicated monitoring stations during 1969-1972.* Level A = original first-stage health warning level. Level B = approximate current first-stage level (0.20 ppm,UV method). Exacerbation of asthma found in 2-hr exposures at this concentration in 2 subjects. Level C = original second-stage alert level. Symptoms and physiological changes found in 2-hr exposures at or slightly below this concentration in various individuals and subject groups. Level D = approximate current second-stage level (0.35 ppm,UV method).

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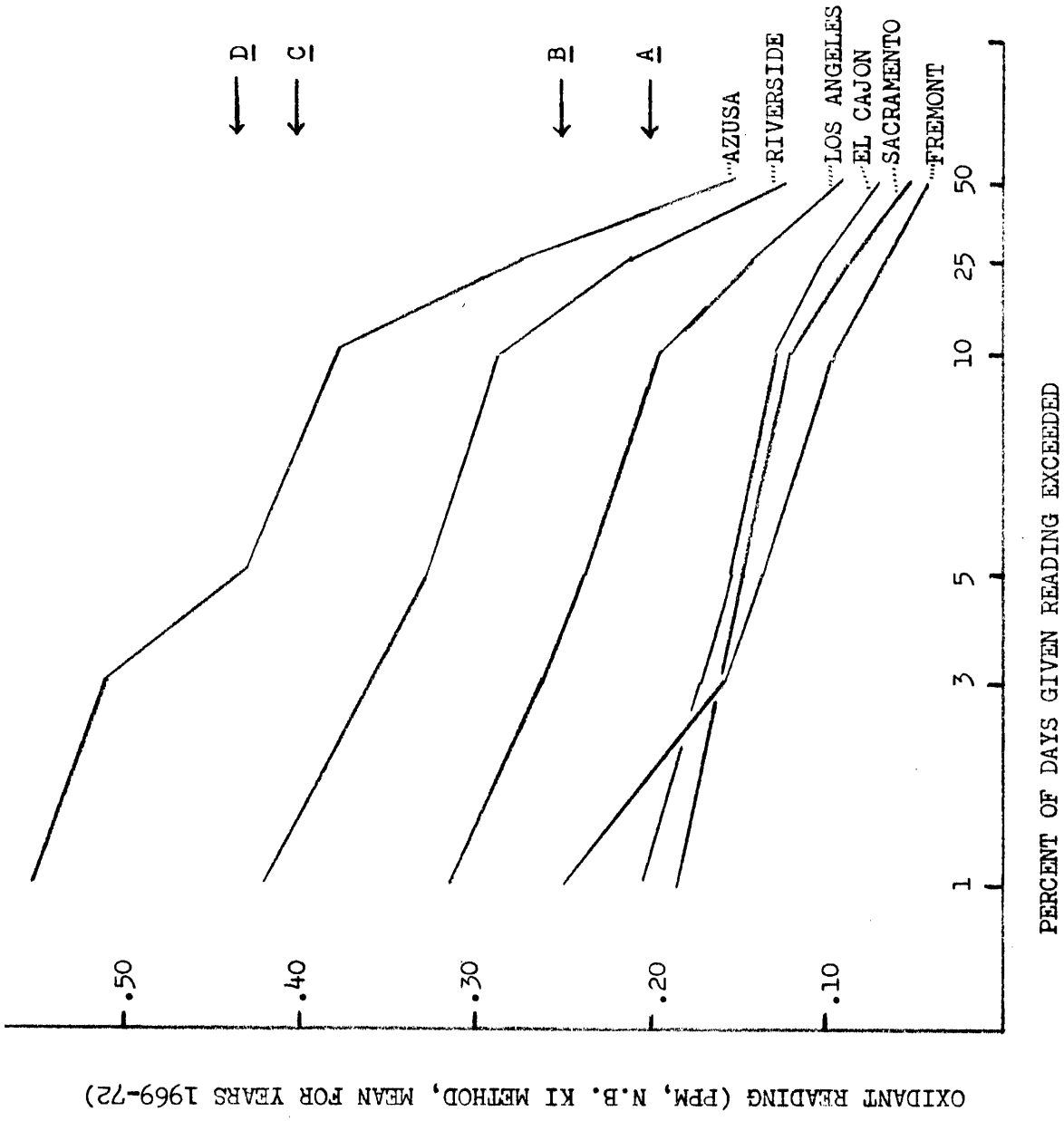
* Source: Ten-Year Summary of California Air Quality Data 1963-1972 California Air Resources Board, Sacramento, 1974.
Azusa and Los Angeles readings multiplied by 1.3 to provide approximate correction for calibration differences (Reference 18).

FIGURE 1.


D
C
B
A
AZUSA
RIVERSIDE
LOS ANGELES
EL CAJON
SACRAMENTO
FREMONT
1
3
5
10
25
50
PERCENT OF DAYS GIVEN READING EXCEEDED
.50
.40
.30
.20
.10
OXIDANT READING (PPM, N.B. KI METHOD, MEAN FOR YEARS 1969-72)

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GLOSSARY

AC (or AcChase)	Acetylcholinesterase (in red blood cells)
aw	Airways
FEV_1	One-second forced expiratory volume
FRC	Functional residual capacity
FVC	Forced vital capacity
KI	potassium iodide
MMF	Maximum midexpiratory flow rate, 25% - 75% FVC
NO_2	Nitrogen dioxide
O_3	Ozone
PPM	Parts per million, by volume
RBC F	Red blood cell fragility
R_t	Total pulmonary resistance, forced-oscillation method
SG	Specific conductance
SS	Symptom score
TLC	Total lung capacity
$\dot{V}_{max}$	Peak expiratory flow rate
$\dot{V}_{50}$	Maximum expiratory flow rate, 50% FVC
$\dot{V}_{25}$	Maximum expiratory flow rate, 25% FVC

Hosp. #_____

Subject #_____

PSA Project #_____

PROFESSIONAL STAFF ASSOCIATION

RANCHO LOS AMIGOS HOSPITAL

HUMAN CONSENT FORM

Subject's Name:_____ Date:_____

FORM FOR OBTAINING INFORMED CONSENT FOR INDIVIDUAL SUBJECTS

The following will be carefully read and signed by each participating subject:

(1) You are being asked to participate in a study to determine whether air pollution can influence human physiological or behavioral functions and the results from this study will help determine any such effects. This information is needed to more accurately assess observed and claimed symptomatic effects from air pollutants in the Los Angeles Area.

The nature of this study is as follows:

You will be asked to remain within the chamber for periods of approximately two hours. At this time, ozone will be put into the air entering the chamber. Also, the temperature and humidity may be elevated so as to be about like a smoggy summer day. During this period, you will be asked to intermittently exercise and rest. At the end of the exposure period, you will be requested to perform a variety of tasks under controlled conditions. At all times you will be carefully monitored by technical specialists and a physician, who will be in charge and constantly available. Most of the tests will not be especially demanding, but may require several hours of your attention and time and include, essentially, measures of respiration and breathing mechanics. Every effort will be made to provide for your comfort during the time of your test. Your response will be carefully monitored.

Do you have any questions? If not, please indicate your understanding by initialing below:

Initial_____ Date_____

(2) Other than obtaining venous blood specimens, no test instrument that could cause pain will be used.

During the test procedures you will be requested to breathe into a container and to perform other breathing tests. The data will be kept in confidential files. Reporting information will not be made in terms of subjects' names.

Are there any questions? If not, please initial here:

Initial_____ Date_____

(3) Immediate and long-term benefits will include:

(a) Supportive data for defining possible effects of atmospheric pollutants.

(b) Data will be available from the physiological and clinical tests. A summary of this information will be provided your physician upon request.

(c) Knowledge concerning the exact influence of oxidant pollution on your asthmatic condition which may modify ideas about where to live, work, etc.

In general, the potential usefulness of these data in regard to preventive medicine are appreciable and therefore, your cooperative efforts in the study will be most important.

Are there any questions regarding the possible benefit to be derived? If not, please indicate by initialing below:

Initial_____ Date_____

(4) The study will provide thorough monitoring of medical effects and every effort will be made to carefully select participants, however there exists the possibility that this exposure may provoke an asthmatic attack. If this occurs you will be under constant supervision by a physician and proper and expert treatment will be given. At all times during the course of this study, you will be able to stop or discontinue your participation. The stopping of the study by you will in no way affect your care by your physician here or elsewhere. Since communication will always be available, you merely have to notify the attendant technician of your desire and the study will be discontinued.

Are there any questions regarding your ability to discontinue participation in the study? Also, if there are any questions at all regarding what will be done, please understand that you are free to consult with the attendant technician or physician. If you have no questions regarding your ability to discontinue participation in the study at any time, initial below:

Initial_____ Date_____

(5) As detailed above, elaborate precautions will be taken to prevent hazards. Barring unlikely problems, the hazards are similar to those you would encounter while working in your yard (e.g., mowing grass, gardening) on a smoggy summer day. That is you will not be exposed to conditions more dangerous than what are likely to occur in the Los Angeles basin on a summer day.

On the other hand, continuous monitoring of the electrocardiogram and other intermittent tests adds greatly to safety in a way that is comparable to that provided in a hospital intensive care unit. Thus, we feel the minimal risk is more than compensated for by the enhanced safety factors.

I understand I will be informed of any changes in the nature of the study or in the procedures as described above, as they may occur.

Do you have any questions regarding the assessment of possible hazards? Please indicate that the previous material is clear and acceptable by signing below:

Signed:_____ Date_____

I have explained and discussed each part with the patient and have questioned him to evaluate his comprehension. I believe that he/she understands all parts of this document.

Witness:_____, MD Date_____